Krieg Claim 7 (U.S. 6,207,646)	**Carson Claim 202**
A composition comprising: a plasmid including an immunostimulatory nucleic acid sequence,	A composition comprising: a plasmid including an immunostimulatory nucleic acid sequence
comprising: 5'$X_1X_2CGX_3X_4$3' wherein C is unmethylated, wherein X_1, X_2, X_3, and X_4 are nucleotides and an antigen in a pharmaceutically acceptable carrier, wherein X_1X_2 are nucleotides selected from the group consisting of: GpT, GpG, GpA and ApA; and X_3X_4 are nucleotides selected from the group consisting of: TpT, CpT, GpT, and TpG.	comprising: AACGTT wherein C is unmethylated, and an antigen in a pharmaceutically acceptable carrier, wherein the antigen is encoded in the plasmid.

New claim 202 is a substantial copy of claim 7 (plasmid containing immunostimulatory CG-containing sequence AACGTT) in conjunction with claim 10 (wherein the antigen is encoded in a DNA vaccine) of the Krieg '646 patent. Thus, both claim 202 and claim 7 recite a CG-containing sequence. Claim 202 imports a substantial copy of the limitation of claim 10 of the Krieg '646 patent, namely, that the antigen is encoded in a DNA vaccine. Claim 202 recites that the antigen is encoded in the plasmid. As is well known in the art, a DNA vaccine is a polynucleotide vector, typically a DNA plasmid, comprising a sequence that encodes an antigen of interest, which antigen is in turn expressed in the host to generate an immune response. Thus, had claim 10 of the Krieg '646 patent depended upon claim 7 instead of claim 6, Applicants' claim 202 would have been almost an exact copy of that claim.

One question raised during the interview was whether the term "antigen" in claim 7 of the Krieg '646 patent encompasses an antigen encoded by a nucleic acid. As discussed above, dependent claim 10 of the Krieg '646 patent recites that the "antigen is encoded in a DNA vaccine." During the interview, the Examiner indicated agreement that the term "antigen" encompassed an antigen encoded by a nucleic acid such as in a DNA vaccine. Furthermore, the specification of the Krieg '646 patent states that "[w]hen the vaccine is a DNA vaccine at least

two components determine its efficacy. First, the antigen encoded by the vaccine determines the specificity of the immune response. Second, if the backbone of the plasmid contains CpG motifs, it functions as an adjuvant for the vaccine." Col. 33, lines 38-42. Moreover, Applicants respectfully remind the Office that the test for determining whether claims are directed to the same invention is whether one claim is anticipated or rendered obvious in view of the other claim. 37 C.F.R. § 1.601(n). In this context, an "antigen" and an antigen encoded by a nucleic acid sequence are obvious variants.

New claim 203 recites a species of claim 202, namely, pREP7 encoding an antigen. There is no corresponding claim in the Krieg '646 patent.

B. New claim 204 and corresponding claim 3 in the Krieg '646 patent are directed to the same invention

Pending claim 204 is a substantial copy of claim 3 of the Krieg '646 patent.

The following chart provides a side-by-side comparison of claim 3 of the Krieg '646 patent and new claim 204.

Krieg Claim 3 (U.S. 6,207,646)	**Carson Claim 204 ('191)**
A method for desensitizing a subject against the occurrence of an allergic reaction in response to contact with a particular allergen,	A method of treating an allergy in a vertebrate,
comprising administering to the subject an effective amount of an immunostimulatory nucleic acid,	comprising administering to the vertebrate an effective amount of an immunostimulatory nucleic acid in a plasmid,
comprising: $5'X_1CGX_23'$ wherein the immunostimulatory nucleic acid includes at least 8 nucleotides and wherein C is unmethylated and wherein X_1 and X_2 are nucleotides	said immunostimulatory nucleic acid comprising 5'CG3', wherein C is unmethylated,
and an effective amount of the allergen.	and an effective amount of an antigen which stimulates production of allergy-associated IgE antibodies in the vertebrate, wherein said antigen is encoded in the plasmid.

Appendix A provides a discussion of why these claims are directed to the same invention. In summary:

- Both claim preambles are directed to a method of treating an allergy, which, as is well-known in the art, involves an effort to desensitize a subject or vertebrate such that the extent of an allergic reaction is reduced upon exposure to the offending antigen (allergen).
- The Krieg '646 patent specification refers to "desensitization therapy for allergies." Col. 34, lines 6-9; *see also* col. 6, lines 62-65, and col. 34, lines 18-26.
- Both preamble recitations aim for the same goal that is well recognized in the art: reduction of allergy-associated IgE antibodies, which mediate the unpleasant symptoms of allergy (such as histamine release, leading to runny eyes, itching, etc.). While Applicants' recitation is more concise than that of claim 3 of Krieg '646, both convey the same concept and objective via reduction of allergy-associated IgE production.
- Claim 3 of the Krieg '646 patent recites that the recipient of the treatment is a "subject", which is defined in the specification as "a human or vertebrate animal..." Col. 13, lines 27-29. Applicants' claim 204 recites "vertebrate".
- A plasmid is an obvious polynucleotide species in view of a polynucleotide of at least 8 nucleotides in length, and vice versa. In a plasmid, the recitation of X_1, X_2, etc. is rendered superfluous, as the CG sequence would *de facto* always be flanked by other nucleotides. The recitation of at least 8 nucleotides is also rendered superfluous, as a plasmid must have at least 8 nucleotides. Conversely, a plasmid anticipates a polynucleotide of at least 8 nucleotides in length.
- Claim 3 of the Krieg '646 patent recites "allergen". One skilled in the art would readily recognize that an allergen is an antigen that stimulates an allergic response, and that an allergy in turn is an inappropriate immune response to the offending antigen.

- It is also well known in the art that a hallmark of an allergic response is production of allergy-associated IgE antibodies in the subject having the allergic reaction. The Krieg '646 patent specification states that allergies "are generally caused by IgE antibody generation". Col. 34, lines 7-9. Thus "allergen" and "an antigen which stimulates production of allergy-associated IgE antibodies" are essentially the same recitations.
- Claim 3 of the Krieg '646 patent recites that an "allergen" is administered. Applicants' claim recites an obvious variation of administering the offending antigen, namely, that the antigen is encoded in the plasmid. Conversely, administering an antigen *per se* is obvious in view of administering an antigen which is encoded in a plasmid (polynucleotide). One of ordinary skill would recognize that the delivery of an antigen encoded by a plasmid is an obvious alternative with respect to delivery of antigen *per se*. In terms of result, both an "antigen" and an "antigen encoded in a plasmid" stimulate an antigen-specific immune response. Applicants also point out that claims of the Krieg '646 patent use these terms interchangeably.

Applicants wish to point out that to provoke an interference, claims of the Krieg '646 patent were substantially copied. Thus, most claim limitations are those that were examined and approved by the Examiner who allowed the Krieg '646 patent. Applicants' claims and the Krieg claims discussed above are directed to the same invention.

III. Compliance with 37 C.F.R. § 1.607(a)(2): Presenting a proposed count

Applicants present proposed counts 1 and 2 in Appendix B, each of which is formulated in the alternative.

A. Discussion of Proposed Count 1

The first alternative is identical to Applicants' claim 202. The second alternative is identical to claim 7 of the Krieg '646 patent, and differs insubstantially from the first alternative, as discussed below.

Both alternatives recite "a plasmid including an immunostimulatory nucleic acid sequence". Both alternatives recite that the immunostimulatory sequence contains a "CG" dinucleotide sequence and that the C is unmethylated.

The first alternative recites nucleotide sequences flanking the "CG" dinucleotide sequence as "AA" and "TT", which is identical to a species recited in claim 7 of the Krieg '646 patent and in the second alternative. The second alternative recites that flanking sequences X_1X_2 are selected from the group consisting of GpT, GpG, GpA, and ApA; and that flanking sequences X_3X_4 are selected from the group consisting of TpT, CpT, GpT, and TpG. Applicants also point out that, in the context of a plasmid, which is circular DNA, there must always be flanking nucleotides with respect to a "CG" found in that plasmid.

The first alternative recites that the antigen "is encoded in the plasmid". The second alternative recites an "antigen". In this context, the phrases are equivalent and not patentably distinct (*i.e.*, are obvious variants). The Examiner is referred to the above discussion and Appendix A comparing Applicants' claim 204 particularly the subsection "wherein said antigen is encoded in the plasmid" and Krieg claim 3, which is applicable to comparing the proposed counts and reaching the conclusion that the proposed counts are substantially the same and are directed to the same invention.

B. **Discussion of Proposed Count 2**

The first alternative is identical to Applicants' claim 204. The second alternative is identical to claim 3 of the Krieg '646 patent and differs insubstantially from the first alternative. As discussed above and in Appendix A, new claim 204 and claim 3 of the Krieg '646 patent are directed to the same invention. Therefore, it is proper to include them as two alternatives of the same count.

IV. Compliance with 37 C.F.R. § 1.607(a)(3): Identification of claims of the Krieg '646 and '388 patents which correspond to the proposed counts

A. Proposed Count 1

1. Krieg '646 patent claims 1-2, 4, 6-11, 13-37, and 39 correspond to proposed count 1

Applicants identify claims 1-2, 4, 6-11, 13-37, and 39 of the Krieg '646 patent as corresponding to proposed count 1. Appendix C provides a claim-by-claim explanation as to why these Krieg '646 patent claims correspond to proposed count 1. For the Examiner's convenience, the composition claims are presented first, followed by the method claims. Applicants submit that the method claims are obvious in view of proposed count 1 directed to the immunostimulatory compositions and thus correspond to the count.

2. Krieg '388 patent claims 1-2, 4, 6-9, 13-19, and 21-22 correspond to proposed count 1

Applicants identify claims 1-2, 4, 6-9, 13-19, and 21-22 of the Krieg '388 patent as corresponding to proposed count 1. Appendix D provides a claim-by-claim explanation as to why these Krieg '388 patent claims correspond to proposed count 1. For the Examiner's convenience, the composition claims are presented first, followed by the method claims. Applicants submit that the method claims are obvious in view of proposed count 1 directed to the immunostimulatory compositions and thus correspond to the count.

B. Krieg '646 patent claims 3, 11, 12, 17, 21, 25, 27, 37, and 38 correspond to proposed count 2

Applicants identify Krieg '646 patent claims 3, 11, 12, 17, 21, 25, 27, 37 and 38 as corresponding to proposed count 2. All of these dependent claims are directed to compositions containing an allergen. Appendix E provides a claim-by-claim explanation as to why these Krieg '646 patent claims correspond to proposed count 2. As a preliminary matter, claims 11, 17, 21, 25 and 37 recite Markush groups which recite, inter alia, "allergen" as a species of antigen, and to the extent "allergen" is contained in the Markush group these claims correspond to the count, as discussed more fully in Appendix E. Applicants submit that the above claims do not define separate patentable inventions within the meaning of 37 C.F.R. § 1.601(n).

V. Compliance with 37 C.F.R. § 1.607(a)(4): Presenting claims from the application which correspond to the proposed counts

Applicants identify new claim 202 as corresponding exactly to the first alternative of proposed count 1, and new claim 203 that corresponds substantially thereto.

Applicants identify claim 204 as corresponding exactly to the first alternative of proposed count 2.

VI. Compliance with 37 C.F.R. § 1.607(a)(5): Applying the terms of the application claims corresponding to the proposed count to the disclosure of the application

A. Claims 202 and 203

In Appendix F, Applicants list exemplary support for the limitations of newly presented claims 202 and 203 in the instant application ('191). However, the listing in Appendix F is only exemplary and Applicants expressly reserve the right to refer to additional passages if deemed necessary.

B. Claim 204

In attached Appendix G, Applicants list exemplary support in the instant application ('191) for the limitations of claim 204. However, the listing in Appendix G is only exemplary and Applicants expressly reserve the right to refer to additional passages if deemed necessary.

One issue discussed in the interview was whether treatment of allergy using CG-containing immunostimulatory sequences as claimed was enabled, and in particular the Examiners wanted an explanation of Example VII. First, the specification refers to using such polynucleotides for treatment of allergies, and is thus presumptively enabling. *See, e.g.*, the instant specification on page 4, lines 9-11; page 49, lines 9-10 ("TH1 responses are to be of particular importance in the treatment of allergies and AIDS"); page 5, lines 13-15; and page 36,

lines 1-4. In particular, Example VII shows a reduction of antigen-specific, allergen-associated IgE production in mice receiving an antigen-encoding plasmid that also contains an immunostimulatory, CG-containing sequence.

In this Example, mice were immunized with a plasmid containing an immunostimulatory, CG-containing sequence as well as a sequence encoding β-galactosidase (pCMV-LacZ). In this context (the mouse system), β-galactosidase, a bacterial protein, is a foreign antigen and stimulates production of antibodies, including allergy-associated IgE antibodies ("lacZ antibodies"). As discussed herein and well known in the art, IgE antibodies are indicative of an allergic response. *See, e.g.*, specification on page 49, lines 6-7 ("TH2 responses include the allergy -associated IgE antibody class").

The mice were then boosted with the allergen and IgE antibody levels measured to assess the extents of allergic responses. As shown in Figure 17, the mice that had been immunized with pCMV-LacZ had low anti-LacZ IgE levels, while the mice that had been immunized with the LacZ protein produced 10 times more anti-LacZ IgE than the pCMV-LacZ injected mice. The results are summarized in the specification, "anti-LacZ IgE levels in the plasmid-injected mice were consistently low both before and after boosting [with LacZ antigen]. . . .These data show that the [LacZ] plasmid injected mice developed an antigen specific TH1 response to the plasmid expression product, with concomitant suppression of IgE production. . ." Page 51, lines 23-24, and page 52, lines 6-8. Thus, Applicants respectfully submit that claim 204 is enabled.

Finally, Applicants note that the Krieg '646 specification also connects IgE production with allergy, stating that allergies "are generally caused by IgE antibody generation". Col. 34, lines 7-9.

VII. Compliance with 37 C.F.R. § 1.607(a)(6): Requirements of 35 U.S.C. § 135(b) are met

The claims introduced by this amendment have been presented within one year of issuance of the Krieg '646 patent (which issued March 27, 2001) and the Krieg '388 patent (which issued February 27, 2001). Pre-issuance publication of the patent applications corresponding to the Krieg '646 and '388 patents did not occur, as these applications were filed before November 29, 2000.

VIII. Compliance with 37 C.F.R. § 1.608

Applicants have an earlier effective filing date, and thus should be designated as senior party with respect to both counts. As such, no showing pursuant to § 1.608 is required. Applicants are entitled to priority benefit of the filing date of U.S. Serial No. 08/112,440, filed August 26, 1993, and U.S. Serial No. 08/446,691, filed June 7, 1995, because both prior applications disclose at least a constructive reduction to practice of the species of claim 203, which species falls within the genus of claim 202, and thus proposed count 1.

An exemplary showing of the passages in the grandparent and great-grandparent applications which constitute a constructive reduction to practice of proposed count 1 is set forth in Appendix H. The great-grandparent application U.S. Serial No. 08/112,440 describes AACGTT-containing antigen-encoding plasmids that may be used to generate an immune response. An antigen-encoding plasmid based on the vector pREP7, which is a species of claim 202, is described in the instant application on page 26, lines 5-6, the grandparent application U.S. Serial No. 08/446,691, on page 33, lines 1-2, and the great-grandparent application U. S. Serial No. 08/112,440, on page 23, lines 17-18 (and in Example I). The great-grandparent specification also states that this plasmid was publicly available from Invitrogen (San Diego, CA) at page 23, lines 17-18. A map of pREP7 from Invitrogen is provided in Appendix I. This plasmid contains an ampicillin resistance gene, which in turn contains the immunostimulatory CG-containing sequence AACGTT. Construction of an antigen-expressing vector pREVk3 based on pREP7 is disclosed in Example I (pages 32-33). The antigen-encoding insert in the pREP7 is Humkv325,

a rearranged kappa light gene from a human patient with chronic lymphocytic leukemia. Thus, the great-grandparent application (U.S. Serial No. 08/112,440), having a filing date of August 26, 1993, discloses an antigen encoding plasmid having the immunostimulatory sequence AACGTT, which appears in the first alternative of proposed count 1.[2]

The Krieg '646 patent issued from U.S. Serial No. 08/738,652, filed October 30, 1996, which claims priority benefit from U.S. Serial No. 08/386,063 (filed February 7, 1995), and U.S. Serial No. 08/276,358 (filed July 15, 1994). The Krieg '388 patent issued from U.S. Serial No. 08/386,063 (filed February 7, 1995), which is the immediate parent of the specification which gave rise to the Krieg '646 patent, and which claims priority benefit of U.S. Serial No. 08/276,358 (filed July 15, 1994).

Applicants are entitled to a filing date of August 26, 1993, which is eleven (11) months before the earliest U.S. filing date (July 14, 1994) of the application which matured into the Krieg '646 patent and the Krieg '388 patent. There is thus no requirement for Applicants to submit a statement that there is a basis upon which Applicants are entitled to a judgment relative to the Patentee. Nor is any showing pursuant to 37 C.F.R. § 1.608(b) required.

IX. Establishing Applicant as Senior Party in accordance with 37 C.F.R. § 1.601(m)

With respect to proposed count 1, neither of the two parent cases of the Krieg '646 patent contains any disclosure pertaining to plasmids (as recited in the proposed count 1). The same is true with respect to the Krieg '388 patent. Thus the earliest date to which Krieg is entitled for proposed count 1 is October 30, 1996, whereas Applicants are entitled to a filing date of August 26, 1993, for proposed count 1.

With respect to proposed count 2, although the Krieg '646 patent claims priority benefit from U.S. Serial No. 08/386,063 (filed February 7, 1995), and U.S. Serial No. 08/276,358 (filed

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[2] As described in the instant specification, the sequence AACGTT is immunostimulatory. *See,* e.g., page 11, line 15 to page 13, line 2, and cited Examples.

July 15, 1994), neither of the two parent cases contains any disclosure pertaining to claim 3 or the allergen-containing compositions (and methods) of claims 11, 12, 17, 21, 25, 27, 37 and 38 of the Krieg '646 patent or of proposed count 2. Thus, the effective filing date of this claimed subject matter is October 30, 1996, whereas Applicants are entitled to the earlier January 30, 1996, filing date of the U.S. Serial No. 08/593,554, for proposed count 2.

Related Krieg patent applications

Applicants wish to bring to the Examiner's attention U.S. Serial Nos. 09/337,893, and 09/337,584. According to the prosecution history of the Krieg '646 patent (*see* amendment dated September 15, 1999; paper no. 19, in conjunction with amendment dated December 22, 1998; paper no. 12, which presents claims referred to in paper no. 19, copies attached as Appendix J), each of these applications contains at least one claim that is related to proposed count 2. The Examiner is respectfully requested to review the related Krieg applications to determine whether claims in those applications should be involved in the requested interference.

CONCLUSION

Applicants are presumptively the prior inventors of the claimed subject matter and desire that an interference be declared using the proposed counts 1 and 2 set forth above. Applicants further submit that the following claims correspond to the proposed counts: claims 1-2, 4, 6-11, 13-37, and 39 of the Krieg '646 patent, claims 1-2, 4, 6-9, 13-19, and 21-22 of the Krieg '388 patent, and claims 202 and 203 of the instant application, correspond to proposed count 1; and claims 3, 11, 12, 17, 21, 25, 27, 37, and 38 of the Krieg '646 patent, and claim 204 of the instant application correspond to proposed count 2. The Applicants' opportunity to prove that they are the actual prior inventors should not be unduly delayed.